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A facile synthesis of novel optically active *R*,*R*-2-(4-(2-(4-(5-chloro-3-halo-pyridin-2-yloxy)-phenoxy)-propionyloxy)-phenoxy)-propionic acid esters using cyanuric chloride as potential herbicide

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Abstract

A facile method for the synthesis of a new series of *R*,*R*-2-(4-(2-(4-(5-chloro-3-halopyridin-2-yloxy)-phenoxy)-propionyloxy)-phenoxy)-propionic acid ester derivatives containing a halo-substituted pyridine carrying two *R*,*R* chiral centers from (*R*)-2-(4-hydroxyphenoxy)propionic acid, halopyridines and alcohols using base/cyanuric chloride/catalyst system is reported. Their herbicidal activities against grass weeds and crops selectivity were evaluated.

Keywords: Aryloxyphenoxypropionic acid; Chiral herbicide; Cyanuric chloride; Esters; *R*,*R*-Diastereomer

Modern high-yield agriculture relies on the effective control of pests and weeds to increase crop quality and yield. Aryloxyphenoxypropionate herbicides (APPHs) have been an interesting and highly effective class of herbicides in the international market over the past decade. Up to now, more than 20 kinds of APPHs, such as clodinafop propargyl, are commercialized all over the world [1]. They are used effectively in a number of crops including soybeans and cereal grains, such as wheat and rice, to control grass weeds [2]. APPH act *via* blocking the biosynthesis of fatty acids by inhibiting acetyl-coenzyme A carboxylase [3,4]. However, continuous application of APPH has resulted in evolution of weeds resistant [5] that means we need novel structure herbicides. Exploration of the structure–activity relationships for the APPH by many agrochemical companies has led to the discovery of herbicides which vary only in the type of aryl or alkyl group of the propionate ester moieties. All of these compounds contain one chiral *R* center that comes from *R*-propionic acid portion of the molecule, and this chiral center is essential to the observed biological effectiveness. It is well known that the *R* isomers of APPH have far greater herbicidal activity than the corresponding *S* isomers [6].

Traditional APPHs have been prepared by coupling alcohols and acid chlorides generated from the parent carboxylic acid [7]. The typical reagents employed to prepare an acid chloride from a carboxylic acid are corrosive $SOCl_2$, PCl_3 or toxic phosgene. This method suffers from several disadvantages and can be cumbersome in a pilot

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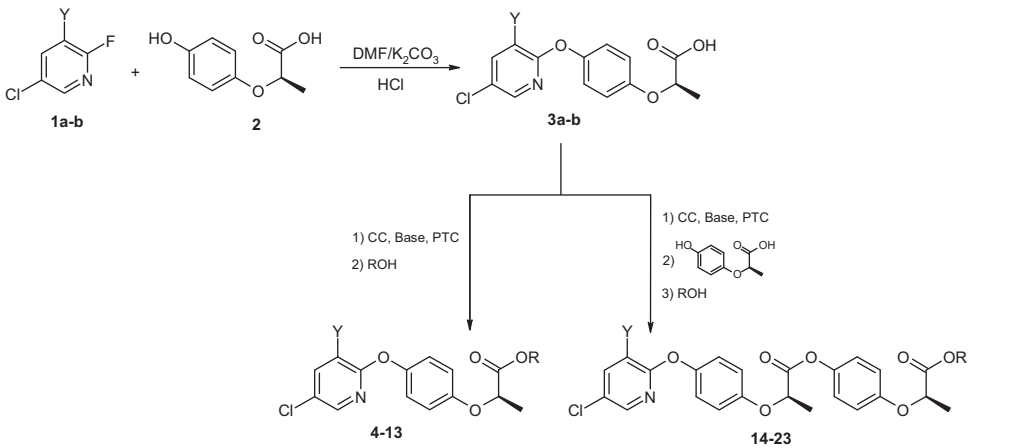
plant. Due to the vigorous conditions and formation of strong acid during the process, sensitivity of optically active carboxylic acids and the disadvantages associated with the use of acid chlorides, esterification of carboxylic acids is an active area of research. A common approach involves treatment of the carboxylic acid with a reagent to form an activated intermediate, which is then treated *in situ* with an alcohol to form the ester product. Carboxylic acids activated by cyanuric chloride (CC) have been used in many chemical transformations [8–10] and can be a valid alternative route to the classical preparation method of APPH. In this article, we have developed a facile process suitable for large-scale preparation of APPH using carboxylic acids, CC as a mild and inexpensive reagent and benzyltriphenylphosphonium bromide (BTPPB) as a phase transfer catalyst (PTC).

On the other hand, to the best of our knowledge the synthesis of aryloxyphenoxypropionic esters containing double *R*,*R* chiral center has not been reported and previous studies were based upon using one *R* chiral spacer between aryl and ester groups. In this study, we have tried to develop new herbicides based on biochemical reasoning and report the synthesis of new titled compounds by introducing second chiral *R* center which can be used as bioisosteric group in order to obtain better herbicidal activity (Scheme 1).

1. Results and discussions

Initially, halo pyridines **1a–b**, *R*-2-(4-hydroxyphenoxy) propionic acid **2**, *R*-2-(4-(5-chloro-3-halopyridin-2-yloxy)-phenoxy)-propionic acids **3a–b** was prepared according to the literature methods [11,12]. The *R* chiral compounds **4–13** and novel final target compounds **14–23** were synthesized from the compounds **3a–b**, CC, base, PTC, ROH in an inert solvent (Scheme 1). New products **14–23** were characterized by ^{1}H NMR, ^{13}C NMR, FT-IR, MALDI-TOF-MS spectroscopy and elemental analysis, which are given in Section 2 [13].

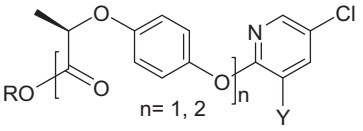
The herbicidal activities of the new compounds **14–23** were evaluated at a rate of 125 g a.i./ha in a set of experiment in greenhouse according to the known method [14] and compared to the results obtained in distilled water and monochiral compounds **4–13** (from which some are the commercially available herbicides). They were tested for post-emergence inhibitory effect against *Alopecurus myosuroides* (*Alo*), *Echinochloa cruss-galli* (*Ech*), *Avena fatua* (*Ave*) weeds. The seed of weeds were collected from different provinces exhibited resistance to commercial herbicides. Inspection of Table 1 reveals that fluorine-containing compounds displayed much better herbicidal activities than chlorine-containing compounds. For example, compounds **14–16** showed higher inhibition rate in comparison to **20–22**. Ethyl ester showed better herbicidal activity than the corresponding methyl ester and *n*-propyl ester in general. The presence of propargyl ester was useful for the improvement of herbicidal activity and selectivity for crop protection. Propargylester **19** showed better inhibition rate against the *A. fatua* and *A. myosuroides* grass in comparison to propylester **16**. It is also interesting to note that in many cases the introduction of second chiral center as *R*,*R* diastereomer slightly increase herbicidal activity and improved crop selectivity. As results listed in Table 1,



R = -CH_3, -CH_2CH_3, -$CH_2CH_2CH_3$,-$CH(CH_3)_2$ -$CH_2CH_2CH_2CH_3$, -CH_2-C ≡ CH; Y= Cl, F

Scheme 1.

Table 1
Herbicidal activity of compounds **4**–**13** and **14**–**23** homologues (relative inhibition of growth percent for post-emergence treatment)/dosage 125 g a.i./ha.



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No.	*n*	R	Y	Yield (%)	Barley	Wheat	*Alo*	*Ech*	*Ave*
4	1	Me	F	85	35	10	75	80	90
14	2	Me	F	82	10	0	80	80	90
5	1	Et	F	87	27	5	82	75	90
15	2	Et	F	78	10	0	90	80	93
6	1	^{n}Pr	F	84	35	10	76	62	84
16	2	^{n}Pr	F	81	15	0	79	70	89
7	1	^{iso}Pr	F	83	30	10	73	57	81
17	2	^{iso}Pr	F	80	12	0	78	65	85
8	1	^{n}Bu	F	85	25	15	54	55	62
18	2	^{n}Bu	F	82	10	5	62	54	63
9[a]	1	Propyn	F	83	20	0	88	82	95
19	2	Propyn	F	80	0	0	100	92	100
10	1	Me	Cl	86	30	10	30	40	30
20	2	Me	Cl	82	15	0	42	44	43
11	1	Et	Cl	88	25	10	45	51	50
21	2	Et	Cl	83	15	0	52	54	54
12	1	^{n}Pr	Cl	85	18	15	35	40	45
22	2	^{n}Pr	Cl	82	10	0	36	45	50
13	1	Propyn	Cl	83	20	0	57	45	47
23	2	Propyn	Cl	80	5	0	60	53	50

[a] Herbicidal activity of clodinafop propargyl a commercially available herbicide has been evaluated for comparison.

fluorine-containing compound **19** that included propargyl ester moiety displayed much better herbicidal activity and crop selectivity.

2. Experimental

*2.1. General procedure for the synthesis of compounds (**4–13**)*

N,*N*-Dimethylamino pyridine (DMAP) (0.01 mol) was added to a solution of **3a**–**b** (0.01 mol), 0.01% mol BTPPB, and CC (0.005 mol) in acetone (60 mL) at 25 °C. After stirring for 2 h, the alcohol (0.011 mol) was added to the reaction mixture, and stirred for 2 h. The salt was filtered off and the acetone was removed by rotary evaporator. The crude product poured in an ice water bath, filtered and crystallized in EtOH to the average yield of 85%.

*2.2. General procedure for the synthesis of compounds (**14–23**)*

To the stirred solution of DMAP (0.025 mol), 0.01% mol BTPPB and CC (1.8 g 0.01 mol) in acetone (30 mL), **3a**–**b** (0.01 mol) was added during 10 min and mixed for an hour at 25 °C. Reaction mixture was then treated with **2** (1.82 g, 0.01 mol) for 2 h and followed by the addition of ROH (0.011 mol). After completion of the reaction (about 2–3 h, monitored by thin-layer chromatography, TLC, eluent *n*-hexane:EtOAc 2:1), the mixture was poured on ice water adjusted at pH 8 and the obtained precipitate was filtered and crystallized in EtOH.

For herbicidal activity tests, an emulsion concentrate as EC 8% was formulated by mixing 8 parts of the active ingredients (a.i.), 14 parts of blended emulsifiers MS and FF4 (trade name), 10 part of cyclohexanone, 30 part of pine oil and sun flower oil was added up to 100 mL. Herbicidal testing carried out at the rate of 125 g a.i./ha with a spelling

volume of 1000 L/ha. All the treatments were replicated three times in a completely randomized design. Three weeks after treatment, the plants were cut at the soil surface and their fresh weight was determined. The herbicidal activity was calculated as the inhibition percent in comparison to the distilled water. Range 0% means no effect, 100% means complete killing (Table 1).

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2010.12.001.

References

[1] H.P. Li, Pestic. Sci. Adm. 25 (2004) 28.
[2] K.T. Ren, Y.H. Li, H.Z. Yang, Chin. J. Pestic. 38 (1999) 1.
[3] X.L. Zhu, L. Zhang, Q. Chen, J. Wan, G.F. Yang, J. Chem. Inf. Model 46 (2006) 1819.
[4] X.L. Zhu, G.F. Hao, C.G. Zhang, G.F. Yang, J. Chem. Inf. Model 49 (2009) 1936.
[5] E. Zand, F. BenaKashani, H.M. Alizadeh, et al. Iranian J. Weed Sci. 2 (2006) 17.
[6] R.W. Brown, J. Agric. Food Chem. 8 (1990) 269.
[7] R. Schurter, H. Rempfler, US PT 4,713,109, 1987.
[8] B. Mokhtari, R. Azadi, A. Azhdari, Chin. Chem. Lett. 21 (2010) 171.
[9] K. Venkataraman, D.R. Wagle, Tetrahedron Lett. 32 (1979) 3037.
[10] G. Blotny, Tetrahedron 62 (2006) 9507.
[11] K.Y. Chen, C.T. Huang, Int. J. Appl. Sci. Eng. 2 (3) (2004) 286.
[12] P. Zhong, H. Hu, S. Guo, Synth. Commun. 34 (2004) 4301.
[13] Selected data of compounds: (*R*,*R*)(+)-2-(4-(5-chloro-3-fluoropyridin-2-yloxy)phenoxy)propionic acid 4-(1-methoxycarbonylethoxy)phenyl ester (**14**): Yield 82%, $[\alpha]^{20}_{D}$ +90 (acetone, c 2), mp 75–76 C. ^{1}H NMR: 7.88 (s, 1H), 7.52 (d, 1H), 7.20 (d, 2H, *J* = 8.7 Hz), 7.05 (d, 2H, *J* = 8.7 Hz), 6.98 (d, 2H, *J* = 8.7 Hz), 6.85 (d, 2H, *J* = 8.7 Hz), 4.94 (q, 1H, *J* = 6.5 Hz), 4.73 (q, 1H, *J* = 6.5 Hz), 3.75 (s, 3H), 1.78 (d, 3H, *J* = 6.5 Hz); 1.62 (d, 3H, *J* = 6.5 Hz); IR (max, KBr): 3075, 2950, 1749, 1508, 1226, 1191 cm^{-1}; ^{13}C NMR (100 MHz, $CDCl_3$): 18.5(2C), 52.3, 73.0, 73.2, 115.8, 116.2, 122.1, 122.3, 124.8, 125.0, 140.1, 144.3, 145.2, 147.2, 148.7, 154.8, 155.4, 170.8, 172.4; Calcd. $(M)^+$ *m*/*z* 489.8. Found: MALDI-TOF-MS: (M+Na) + 512.2. Anal. calcd. for $C_{24}H_{21}ClFNO_7$ (489.88): C, 58.84; H, 4.32; N, 2.86. Found: C, 58.64; H, 4.24; N, 2.75. (*R*,*R*)(+)-2-(4-(5-chloro-3-fluoropyridin-2-yloxy)phenoxy)propionic acid 4-(1-ethoxycarbonyl-ethoxy)-phenyl ester (15):Yield 78%, $[\alpha]^{20}_{D}$ + 90 (acetone, c 2), mp 60–62 C. ^{1}H NMR: 7.88 (s, 1H), 7.50 (d, 1H), 7.12 (d, 2H, *J* = 8.6 Hz), 7.01 (d, 2H, *J* = 8.6 Hz), 6.96 (d, 2H, *J* = 8.6 Hz), 6.86 (d, 2H, *J* = 8.6 Hz), 4.94 (q, 1H, *J* = 6.5 Hz), 4.72 (q, 1H, *J* = 6.5 Hz), 4.22 (q, 2H, *J* = 6.9 Hz), 1.78 (d, 3H, *J* = 6.5 Hz); 1.61 (d, 3H, *J* = 6.5 Hz); 1.25(t, 3H, *J* = 6.9 Hz), IR (max, KBr): 3035, 2993, 1758, 1505, 1195, 1099 cm^{-1}; ^{13}C NMR (100 MHz, $CDCl_3$): 14.1, 18.5(2C), 61.3, 73.1, 73.2, 115.9, 116.2, 122.0, 122.3, 124.8, 125.0, 140.1, 144.3, 145.2, 147.2, 148.7, 154.8, 155.5, 170.8, 172.4; Calcd. $(M)^+$ *m*/*z* 504.2. Found: MALDI-TOF-MS: $(M+Na)^+$ 527.2. Anal. calcd. for $C_{25}H_{23}ClFNO_7$ (503.90): C, 59.59; H, 4.60; N, 2.78. Found: C, 59.84; H, 4.64; N, 2.74. Further information is given in Supporting information.
[14] T. Chen, P. Shen, Y. Li, H. He, J. Fluorine Chem. 127 (2006) 291.